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REMARKS

Claims 1-7 have been canceled and claims 33-35 have been amended. Claims 33-36 are therefore presently pending and under consideration. Claims 8-32 and 37-62 are also pending but have been withdrawn from consideration.

Election/Restriction

The Examiner indicated that Applicant's traversal of the Election/Restriction requirement of 7/31/2002, on the ground that groups I and III represented a subcombination/combination, was not found persuasive because the subcombination was not allowable. Nevertheless, the Examiner indicated that claims for the combination would be rejoined in the event that the product becomes allowable.

Applicant appreciates the Examiner's willingness to rejoin the combination claims upon allowance of claims to the subcombination. However, Applicant continues to assert that restriction is improper because a predetermination of allowability is not a requirement for examining subcombination and combination inventions together. If two-way distinctness is demonstrated, as is the case here, claims to the combination should be examined together with claims to the subcombination, and simply be subject to the same prior art-based rejections as the subcombination claims.

As set forth below, Applicant believes that claims 33-36, drawn to the subcombination of Group I (mutated adenoviral fiber protein) are allowable over the prior art of record. Accordingly, Applicant respectfully requests that the combination claims in Group III that depend from claims 33-36 (i.e., claims 38-41, 49, and 61-62) be rejoined and examined along with claims 33-36.

Furthermore, upon rejoinder of the appropriate combination claims of Group III, Applicant respectfully requests that the Office also rejoin the method claims in Groups IV, V, and IV pursuant to *In re Ochiai*.

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Claim Rejections - 35 USC § 112, second paragraph

Claims 4 and 33-36 stand rejected under 35 USC § 112, second paragraph, as being indefinite because of the term "contains." Claim 4 has been canceled and claims 33-35 have been amended to replace this term with "comprises." Accordingly, withdrawal of this rejection is respectfully requested.

Claim Rejections - 35 USC § 102

Claims 1-7 stand rejected under 35 USC § 102(b) as being anticipated by McClelland (U.S. Pat. No. 5,543,328). Without conceding the Examiner's position, Applicant has canceled these claims, rendering this rejection moot. Applicant expressly reserves the right to contest this rejection in a continuing application.

Claims 1-7 and 33-36 stand rejected under 35 USC § 102(e) as being anticipated by Wickham (U.S. Pat. No. 6,455,314). Without conceding the Examiner's position, Applicant has canceled claims 1-7, rendering this rejection moot as to these claims. Applicant expressly reserves the right to contest this rejection of claims 1-7 in a continuing application.

As to claims 33-36, which remain pending, Applicant respectfully traverses. Wickham does not teach or suggest an Ad5 fiber protein with a double mutation at positions 408 and 409. Wickham merely provides several long lists of mutations with instructions to choose at least one of them. For example, at column 7, lines 24-29, Wickham discloses that "the mutant fiber protein comprises at least one replacement mutation of a residue corresponding to residues 408, 409, 412-417, 420, 477, or 487-491 of the native Ad5 fiber protein or at least one deletion mutation of a residue corresponding to residues 474-477 or 489-492 of the native Ad5 fiber protein." Thus, this text in Wickham suggests to choose at least one out of 15 different mutations, which involves 32,767 different possibilities. (The number of ways of picking k unordered outcomes from n possibilities = nCk . $nCk = [n!]/[(n-k)!k!]$.) One of skill in the art would therefore not read Wickham as teaching or suggesting the particular double mutant recited in claims 33-36.

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It bears mentioning that Wickham likewise does not render Applicant's claimed invention obvious. The mutant fiber proteins disclosed in Wickham exhibit reduced affinity for the CAR protein *in vitro*. See, for example, Examples 1 and 2. Furthermore, in Example 10, Wickham discloses *in vivo* administration to mice of alternatively targeted adenoviruses having mutant fibers. This *in vivo* study showed a dramatic reduction in liver transduction compared to adenoviruses with wildtype fibers. Wickham concludes at column 24, lines 28-30: "These results indicate that fiber mutations ablating native cell-receptor binding are effective in greatly reducing native tropism *in vivo*."

Adenoviruses with Applicant's claimed fibers also exhibit reduced transduction *in vitro*. However, adenoviruses with Applicant's claimed fiber proteins transduce liver very efficiently *in vivo*. The inventors of the present invention discovered that, unexpectedly, adenoviruses with modifications at amino acid positions 408 and 409 of the Ad5 fiber protein provide enhanced gene transfer to and expression in hepatocytes in the liver of mice, as compared to adenoviruses with wildtype fibers. See, for example, page 32, line 19, through page 35, line 17. See also, Smith *et al.*, *Molecular Therapy* 5(6): 770-779 (2002), a copy of which is attached hereto. These unexpected *in vivo* results, which are completely opposite to Wickham's, support Applicant's position that the claimed invention is not obvious in view of Wickham.

Withdrawal of the rejection of the claims in view of the Wickham patent is therefore respectfully requested.

Claim Rejections - 35 USC § 103

Claims 33-36 stand rejected under 35 USC § 103(a) as being unpatentable over Kirby. Kirby is alleged to disclose Ad5 fiber proteins with mutations at residues 408 and 409; however, the Examiner acknowledges that Kirby does not disclose a double mutant that contains both changes. The Examiner alleges that it would have been routine laboratory experimentation by one of skill in the art to examine combinations of known mutants to determine if combinations reduced binding/transduction of CAR. Therefore, the Examiner alleges that it would have been *prima facie* obvious to make a mutant fiber protein with residues 408 and 409 as taught by Kirby. Applicant respectfully traverses.

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A. Legal Requirements for Obviousness

Both the burden of proof and the evidentiary standard for determining obviousness are precisely defined. Specifically, the Examiner bears the burden of presenting a *prima facie* case for obviousness, with a showing of such *prima facie* obviousness requiring: 1) some suggestion or motivation, either in the reference itself or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; 2) the teaching or suggestion of all the claim limitations of the Applicant's invention in the modified or combined prior art references; and, 3) a reasonable expectation of success. MPEP § 2143.

With regard to the first of these factors, suggestion or motivation to modify or combine, such motivation may be found "where there is some teaching, suggestion, or motivation ... either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art." MPEP § 2143.01 (citing *In re Kotzab*, 217 F.3d 1365, 1370 55 USPQ2d 1313, 1317 (Fed. Cir. 2000)). Not only must such motivation be present, it must be specific. The Federal Circuit recently re-emphasized in *In re Lee* the importance of specific motivation, stating:

When patentability turns on the question of obviousness, the search for and analysis of the prior art includes evidence relevant to the finding of whether there is a teaching, motivation, or suggestion to select and combine the references relied on as evidence of obviousness. *See, e.g., McGinley v. Franklin Sports, Inc.*, 262 F.3d 1339, 1351-52, 60 USPQ2d 1001, 1008 (Fed. Cir. 2001) ("the central question is whether there is reason to combine [the] references," a question of fact drawing on the Graham factors).

"The factual inquiry whether to combine references must be thorough and searching." *Id.* It must be based on objective evidence of record. This precedent has been reinforced in myriad decisions, and cannot be dispensed with. *See, e.g., Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1124-25, 56 USPQ2d 1456, 1459 (Fed. Cir. 2000) ("a showing of a suggestion, teaching, or motivation to combine the prior art references is an 'essential component of an obviousness holding'") (quoting *C.R. Bard, Inc., v. M3 Systems, Inc.*, 157 F.3d 1340, 1352, 48 USPQ2d 1225, 1232 (Fed. Cir. 1998)); *In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999) ("Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references."); *In re Dance*, 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637 (Fed.

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Cir. 1998) (there must be some motivation, suggestion, or teaching of the desirability of making the specific combination that was made by the applicant); *In re Fine*, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988) (“teachings of references can be combined only if there is some suggestion or incentive to do so.”) (emphasis in original) (quoting *ACS Hosp. Sys., Inc. v. Montefiore Hosp.*, 732 F.2d 1572, 1577, 221 USPQ 929, 933 (Fed. Cir. 1984)).

In re Lee, 61 USPQ2d 1430, 1433-4 (Fed. Cir. 2002) (vacating and remanding the decision of the Board for failing to follow the relevant precedent).

The fact that the prior art teaches individual elements of the claimed invention that are generally known or within the capabilities of one with knowledge in the art is not, however, sufficient to establish a *prima facie* case of obviousness without any specific teaching or suggestion for making the modification or combination. Accordingly, in a proper analysis of obviousness, the level of knowledge of one with ordinary skill in the art cannot be substituted for a clear suggestion to make a modification or combination. See *A-Site Corp. v. VSI International Inc.*, 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999).

B. The Examiner Has Failed to Provide an Expressed or Implied Motivation to Modify The Cited Reference

The Examiner is required to show how and why Applicant would have been motivated to modify the reference in the manner combined by the Examiner. The Examiner has not done so, but has simply made an unsupported, conclusory statement that “it would have been routine laboratory experimentation by one of skill in the art to examine combinations of known mutants to determine if combinations reduced binding/transduction of CAR.” The Examiner therefore alleges, in essence, that because various fiber mutations were known at the time of the present invention, it would have been *prima facie* obvious to one of ordinary skill in the art to combine them to obtain the specific combination of mutations in the claimed fiber proteins.

Though the motivation to modify prior art does not have to be expressly stated in the reference itself, “the examiner must present a convincing line of reasoning” for a proper conclusion that an invention is obvious in view of prior art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). See also, *Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter.

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1985). In the instant case, the Office Action does not set forth any convincing reasoning as to the rationale behind modifying the cited reference. Indeed, when relying on a “scientific reasoning” rationale for modifying a reference, the Examiner must provide evidentiary support for the existence and meaning of that scientific theory. See, *In re Grose*, 592 F.2d 1161, 201 USPQ 57 (CCPA 1979). Here, the Examiner has failed to meet this burden. The Examiner has neither identified an explicit suggestion in the prior art to modify the reference nor has the Examiner provided the requisite evidence of a scientific rationale for modifying the reference.

In view of the above, Applicant respectfully submits that “it would have been routine experimentation” falls far short of the requisite motivation to modify the cited reference to produce Applicant’s claimed fiber proteins. The Examiner has provided no evidence at all to support the statement purporting to show motivation.

C. There Were Unexpected Results With Applicant’s Claimed Invention

Furthermore, as does the above-discussed Wickham patent, Kirby describes mutant fiber proteins that exhibit reduced affinity for the CAR protein *in vitro*. One would expect that adenoviruses with mutant fiber proteins as described in Kirby would lead to a reduction in *in vivo* liver transduction compared to adenoviruses with wildtype fibers. However, adenoviruses with Applicant’s claimed fiber proteins transduce liver very efficiently *in vivo*. As discussed above, Applicant unexpectedly discovered that adenoviruses with modifications at amino acid positions 408 and 409 of the Ad5 fiber protein provide enhanced gene transfer to and expression in hepatocytes in the liver of mice, as compared to adenoviruses with wildtype fibers. See, for example, page 32, line 19, through page 35, line 17. See also, Smith *et al.*, *Molecular Therapy* 5(6): 770-779 (2002), a copy of which is attached hereto. These unexpected *in vivo* results, which are completely opposite to what one of ordinary skill in the art would expect with Kirby’s mutant fibers, support Applicant’s position that the claimed invention is not obvious in view of Kirby.

In view of the Examiner’s failure to establish the requisite motivation for modifying the Kirby reference in the manner suggested, *prima facie* obviousness has not been established against any of the pending claims. Furthermore, the unexpected *in vivo* results seen with Applicant’s

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claimed invention supports a conclusion that the claimed invention is not obvious in view of Kirby. Applicant therefore respectfully requests that the outstanding rejection under 35 U.S.C. §103(a) be withdrawn.


Conclusion

In view of the above amendments and remarks, it is submitted that this application is ready for allowance. Notice to this effect is solicited at the Examiner's earliest opportunity. If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

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Respectfully submitted,


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